(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 December 2001 (20.12.2001)

PCT

(10) International Publication Number
WO 01/95906 A1

(51) International Patent Classification[7]: A61K 31/426, 31/427, 31/4439, A61P 9/00, 3/10

(21) International Application Number: PCT/GB00/02347

(22) International Filing Date: 16 June 2000 (16.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM P.L.C.** [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **NATHWANI, Ameet** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **RUTTER, Keith**; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/95906 A1

(54) Title: TREATMENT AND PREVENTION OF CARDIAC INSULIN RESISTANCE ASSOCIATED CONDITIONS

(57) Abstract: A method for the treatment or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance, in humans or non-human mammals, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of PPARγ agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof. Conditions associated with cardiac insulin resistance are: microvascular angina, atherosclerosis and congestive heart failure. Compounds include rosiglitazone, troglitazone, englitazone and pioglitazone.

TREATMENT AND PREVENTION OF CARDIAC INSULIN RESISTANCE ASSOCIATED CONDITIONS

This invention relates to a novel treatment and in particular to a method for the treatment and/or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance.

Increases in insulin resistance represent an impairment in the normal biological response to insulin. It is usually associated with conditions such as Type 2 diabetes mellitus where the resistance is primarily manifest in skeletal muscle, adipose tissue and the liver. In certain circumstances however, insulin resistance presents in tissues and organs other than in skeletal muscle and liver and in particular can be present selectively in the heart as cardiac-insulin resistance. In diseases such as cardiac syndrome-X [a form of microvascular angina], or in patients with accelerated atherosclerosis or chronic heart-failure, the increased insulin resistance in the myocardium impairs the ability of the myocardium to rapidly and effectively utilise glucose for metabolism, and may further exacerbate the delicate metabolic balance in this critical tissue. Treatment of cardiac-insulin resistance would be expected to alleviate this metabolic stress and improve the efficiency of glucose uptake, and hence oxidative metabolism of cardiac muscle. Where cardiac muscle is ischaemic and susceptible to hypoxic damage, it is believed that improving the metabolic stress of insulin resistance, will help prevent ischaemic damage to the myocardium.

European Patent Application, Publication Number 0306228 discloses certain thiazolidinedione derivatives which are disclosed *inter alia* as having hypoglycaemic and hypolipidaemic activity and activity in treating certain eating disorders. The compound of example 30 of EP 0306228 is 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione (or 'Compound (I)').

European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione derivatives which are stated to have hypoglycaemic and hypolipidaemic activity.

It is known that the γ-isoform of peroxisome proliferator-activated receptor (herein after PPARγ) is member of a nuclear receptor superfamily that includes receptors for the steroid, thyroid and retinoid hormones(Evans, Science 240, 889-895, (1988)). It is also known from Chawla *et al* that PPARγ is expressed early during the differentiation of adipocytes (Endocrinology 135,798-800, 1994).

It is known from J. Biol. Chem., 270,12963-12966 that thiazolidinediones such as Compound (I) are PPARγ agonists.

USP 5521201 discloses that Compound (I) is useful in the treatment of cardiac disease especially athereosclerosis. Also WO 00/04889 discloses that Compound (I) is useful for reducing post-ischaemic injury of the heart and/or improving the functional recovery of the heart following myocardial ischaemia.

It is now considered that Compound (I) has activity in the treatment or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance. It is therefore of potential use in the treatment or prophylaxis of microvascular angina, atherosclerosis associated with insulin resistance and in the treatment of congestive heart failure, especially in delaying the progression of congestive heart failure, ameliorating or reversing reductions in cardiac muscular endurance and strength associated with congestive heart failure and ameliorating and/or reversing the cachexic phase of congestive heart failure.

Accordingly, the invention provides a method for the treatment or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance, in humans or non-human mammals, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPARγ agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof.

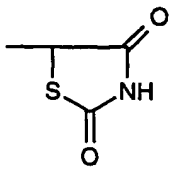
Particular conditions associated with cardiac insulin resistance include microvascular angina and congestive heart failure. A further condition associated with cardiac insulin resistance is atherosclerosis associated with insulin resistance.

A suitable condition associated with cardiac insulin resistance is microvascular angina. A suitable condition associated with cardiac insulin resistance is congestive heart failure.

In the treatment or prophylaxis of congestive heart failure, the present treatment is particularly indicated to delay the progression of congestive heart failure, ameliorate and/or reverse reductions in cardiac muscular endurance and/or strength associated with congestive heart failure and ameliorate and/or reverse the cachexic phase of congestive heart failure.

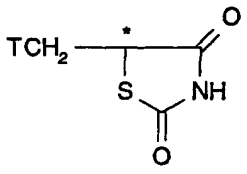
Suitably, the present treatment delays the progression of congestive heart failure. Suitably, the present treatment ameliorates and/or reverses reductions in cardiac muscular endurance and/or strength associated with congestive heart failure. Suitably, the present treatment ameliorates and/or reverses the cachexic phase of congestive heart failure.

Suitable PPARγ agonists include thiazolidinediones, especially thiazolidine-2,4-diones, that is a compound comprising a moiety of formula (A):



(A).

Suitable compounds comprising a moiety of formula (a) include compounds of formula (I):

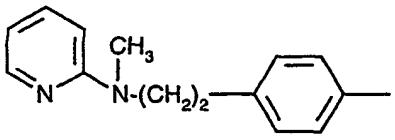


(I)

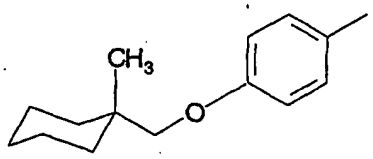
or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein T represents an aryl or heterocyclyl group optionally substituted with one or more alkyl groups, aralkyl groups or heterocyclylalkyl groups, the said alkyl, aralkyl and heterocyclylalkyl groups themselves being optionally substituted.

Suitably, the carbon atom marked with an asterisk (*) in formula (I) is a chiral carbon.

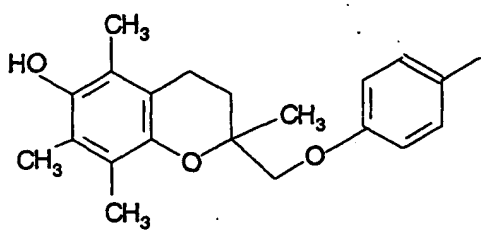
In particular T represents a moiety selected from the list consisting of (a), (b), (c), (d), (e), (f), (g), (h) and (i):



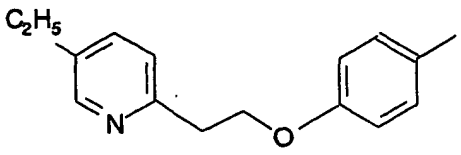
(a)



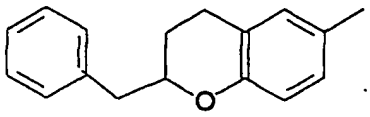
(b)



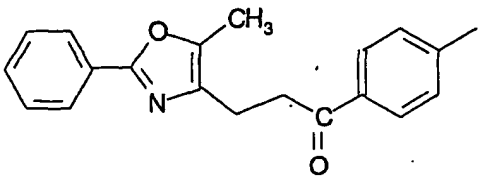
(c)



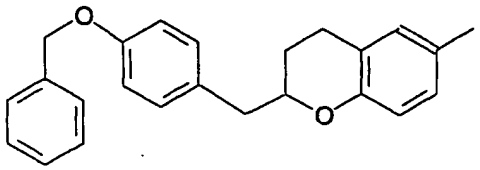
(d)



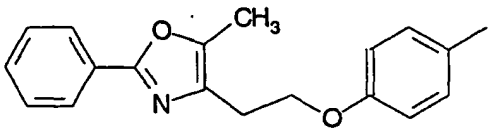
(e)



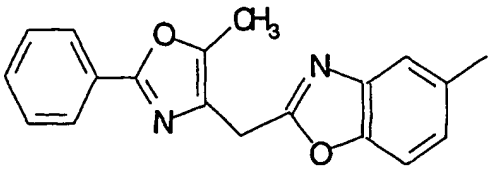
(f)



(g)



(h), and



(I)

In particular should be mentioned the moieties of formula (a), (b), (c), (d) and (e).

Also included in the treatment of the invention are the PPARγ agonists disclosed in European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734 and 0508740, International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, especially the specific example thereof. The contents of these publications are included herein by reference.

Thiazolidinedione PPARγ agonists may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof. Where a PPARγ agonist contains a chiral carbon, and hence exists in one or more stereoisomeric forms or where one or more geometric isomers exist, it will be appreciated that the method of the present invention encompasses all of the said forms of the PPARγ agonists whether as individual isomers or as mixtures of isomers, including racemates.

Particular examples of thiazolidinediones are those disclosed in EP 0306228 and WO94/05659. Further particular examples are the thiazolidinediones disclosed in EP0139421 and USP 5478852.

A preferred thiazolidinedione is Compound (I).

Further particular thiazolidinediones are, (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone)

When used herein the term 'PPARγ agonist' relates to an agonist, such as a small molecular weight agonist, of the peroxisomal proliferator-activated receptor of the gamma subtype, this nuclear receptor is a member of the ligand activated transcription factor family that include the steroid, retinoid and thyroid receptors.

PPARγ agonist activity may be assessed by use of the methodology disclosed by Lehmann et al : Journal of Biological Chem., 270, 12953-12956 (1995).

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

Suitable heterocyclyl groups are aromatic and non-aromatic heterocylic groups.

Suitable non-aromatic heterocylic groups include groups comprising single or fused ring heterocyclic groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen, optionally fused to one or more aryl groups.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 5 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl groups comprise 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable substituents for the heterocyclyl include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

It will be appreciated that where the above mentioned definitions of 'aryl', 'heterocyclyl' and the substituents thereof differ from those in the above mentioned patent publications with respect to the particular compounds disclosed therein, that the definitions in the said publications prevail.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

When used herein the term 'acyl' includes alkylcarbonyl groups.

Suitable alkyl groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable derivatives of a PPARγ agonist are pharmaceutically acceptable derivatives, for example salts and solvates.

Suitable derivatives of any particular PPARγ agonist include those disclosed in the above mentioned publications.

Suitable pharmaceutically acceptable salts include salts of salts derived from appropriate acids, such as acid addition salts, or bases.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine,

glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, a-keto glutarate and a-glycerophosphate, especially the maleate salt.

Suitable pharmaceutically acceptable salts of Compound (I) are as disclosed in EP 0306228 and WO94/05659 and include maleate salts.

Suitable pharmaceutically acceptable solvates include hydrates.

Suitable pharmaceutically acceptable solvates of Compound (I) are as disclosed in EP 0306228 and WO94/05659 and include hydrates.

The PPARγ agonists, such as the thiazolidinediones, referred to herein are conveniently prepared according to the methods disclosed in the above mentioned patent publications in which they are disclosed: Thus Compound (I), or the tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, may be prepared using the processes described in EP 0306228 and WO94/05659.

The salts and/or solvates of the thiazolidinediones may be prepared and isolated according to conventional procedures for example those disclosed in the, above mentioned, patent publications.

The present invention also provides a PPARγ agonist or a pharmaceutically acceptable derivative thereof, for use in the treatment and/or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance.

The present invention also provides a PPARγ agonist or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for the treatment and/or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance.

In the above mentioned method the PPARγ agonist, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

In the treatment of the invention, the PPARγ agonist mentioned herein is formulated and administered in accordance with the methods disclosed in the above mentioned publications, patent applications and patents.

Accordingly, the present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance, which composition comprises a PPARγ agonist, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Suitable dosages of the PPARγ agonist include the known doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Complete Drug Reference (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications or doses which can be determined by standard procedures.

Suitable dosages of the Compound (I) include those disclosed in EP 0306228 and WO94/05659 and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particular dosages of Compound (I) are 2mg, 4mg and 8mg.

Particular dosages of troglitazone include from 100 to 800mg such as 200, 400, 600 or 800mg.

Particular dosages of pioglitazone include from 5 to 50mg, including 10 to 40mg, such as 15, 20, 30 or 40 mg of pioglitazone.

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Complete Drug Reference (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

The activity of compounds in the treatment of the present invention can be determined using known methodology, for example by use of procedures disclosed by Eckel J, Asskamp,B, Reinauer, H (1991) Endocrinology 129, 345-352
Induction of insulin resistance in primary cultured adult cardiomyocytes.

No adverse toxicological effects are expected for the compositions or methods of the invention in the above mentioned dosage ranges.

Claims:

1. A method for the treatment or prophylaxis of cardiac insulin resistance or conditions associated with cardiac insulin resistance, in humans or non-human mammals, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPARγ agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof.

2. A method according to claim 1, wherein a condition associated with cardiac insulin resistance is selected from: microvascular angina, atherosclerosis associated with insulin resistance and congestive heart failure.

3. A method according to claim 1, wherein in the treatment of congestive heart failure there is provided: a delay in the progression of congestive heart failure; an amelioration and/or reversal of reductions in cardiac muscular endurance and/or strength associated with congestive heart failure; or an amelioration and/or reversal of the cachexic phase of congestive heart failure.

4. A method according to claim 1, wherein the PPAR agonist is a thiazolidinedione.

5. A method according to claim 4, wherein the PPAR agonist is selected from the list consisting of: Compound (I), (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone), and 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

6. A method according to claim 4, wherein the PPAR agonist is Compound (I).

7. A method according to claim 4, wherein the PPAR agonist is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 00/02347

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/426 A61K31/427 A61K31/4439 A61P9/00 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HENRY R R: "TYPE 2 DIABETES CARE: THE ROLE OF INSULIN-SENSITIZING AGENTS AND PRACTICAL IMPLICATIONS FOR CARDIOVASCULAR DISEASE PREVENTION" AMERICAN JOURNAL OF MEDICINE, XX, XX, vol. 105, no. 1A, 6 July 1998 (1998-07-06), pages 20S-26S, XP000877433 ISSN: 0002-9343 the whole document --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2001	10/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 05331 A (LIGAND PHARM INC) 12 February 1998 (1998-02-12) abstract page 1, line 14 -page 2, line 5 page 3, line 17 -page 6, line 21 page 16, line 24 -page 19, line 12 page 26, line 1 -page 27, line 10; claims 1-42	1-7
X	US 5 902 726 A (WILLSON TIMOTHY M ET AL) 11 May 1999 (1999-05-11) the whole document	1-7
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 1999 (1999-03) SHIMOYAMA MASAKI ET AL: "Hemodynamic basis for the acute cardiac effects of troglitazone in isolated perfused rat hearts." Database accession no. PREV199900153193 XP002178557 abstract & DIABETES, vol. 48, no. 3, March 1999 (1999-03), pages 609-615, ISSN: 0012-1797	1-5
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 6 July 1998 (1998-07-06) HSUEH WILLA A ET AL: "Cardiovascular risk continuum: Implications of insulin resistance and diabetes." Database accession no. PREV199800429872 XP002178558 abstract & AMERICAN JOURNAL OF MEDICINE, vol. 105, no. 1 PART A, 6 July 1998 (1998-07-06), pages 4S-14S, ISSN: 0002-9343	1-5
X	SHIMABUKURO M ET AL: "CARDIOPROTECTIVE EFFECTS OF TROGLITAZONE IN STREPTOZOTOCIN-INDUCED DIABETIC RATS" METABOLISM, CLINICAL AND EXPERIMENTAL, W.B. SAUNDERS CO., PHILADELPHIA, PA, US, vol. 45, no. 9, September 1996 (1996-09), pages 1168-1173, XP000856580 ISSN: 0026-0495 the whole document	1-6

-/--

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 00/02347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JHA R J: "THIAZOLIDINEDIONES - THE NEW INSULIN ENHANCERS" CLINICAL AND EXPERIMENTAL HYPERTENSION, MARCEL DEKKER, NEW YORK, NY, US, vol. 21, no. 1/2, January 1999 (1999-01), pages 157-166, XP000985778 ISSN: 1064-1963 the whole document	1-7
X	KUEHNLE H F: "NEW THERAPEUTIC AGENTS FOR THE TREATMENT OF NIDDM" EXPERIMENTAL AND CLINICAL ENDOCRINOLOGY AND DIABETES, JOHANN AMBROSIUS BARTH, DE, vol. 104, no. 2, 1996, pages 93-101, XP000605828 ISSN: 0947-7349 the whole document	1-6
X	BAEHR M ET AL: "ACUTE AND CHRONIC EFFECTS OF TROGLITAZONE (CS-045) ON ISOLATED RAT VENTRICULAR CARDIOMYOCYTES" DIABETOLOGIA, BERLIN, DE, vol. 39, July 1996 (1996-07), pages 766-774, XP000856911 ISSN: 0012-186X the whole document	1-6
X	O'KEEFE J H ET AL: "IMPROVING THE ADVERSE CARDIOVASCULAR PROGNOSIS OF TYPE 2 DIABETES" MAYO CLINIC PROCEEDINGS, MAYO MEDICAL VENTURES, ROCHESTER, MN, US, vol. 74, no. 2, February 1999 (1999-02), pages 171-180, XP000856581 ISSN: 0025-6196 abstract page 173, column 1, paragraph 2 -column 2, paragraph 1; figure 1; table 1 page 174, column 1, paragraph 2; figure 2; table 2	1-6
X,P	WO 00 04889 A (BRIL ANTOINE MICHEL ALAIN ;KHANDOUDI NASSIRAH (FR); SMITHKLINE BEE) 3 February 2000 (2000-02-03) abstract page 1, paragraphs 1-3 page 2, paragraphs 3-8 page 5, paragraphs 2,3 page 10, line 3 -page 11, line 33; claims 1-5	1-6

-/--

INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PCT/GB 00/02347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 59586 A (WANG PING H ;UNIV CALIFORNIA (US)) 25 November 1999 (1999-11-25) abstract page 3, line 10 -page 12, line 13; claims 1-10,13-16; examples 1-5	1-7
X	WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) abstract page 1, line 10-19 page 3, line 7,8 page 6, line 3; claims 12,13; examples 1,2	1-6
X	LENHARD, J. M. ET AL: "The RXR agonist LG100268 causes hepatomegaly, improves glycemic control, and decreases cardiovascular risk and cachexia in diabetic mice suffering from pancreatic beta-cell dysfunction" DIABETOLOGIA (1999), 42(5), 545-554 , XP000985788 abstract page 545, column 2, paragraph 1 -page 546, column 1, paragraph 4 page 547, column 2, paragraph 3 -page 548, column 2, paragraph 2; tables 3,4	1-6
X	MURAKAMI T ET AL: "Beneficial effects of troglitazone in vasospastic angina pectoris with diabetes mellitus." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 31, no. 2 SUPPL. A, February 1998 (1998-02), page 411A XP001028258 47th Annual Scientific Session of the American College of Cardiology;Atlanta, Georgia, USA; March 29-April 1, 1998 ISSN: 0735-1097 abstract	1-5
X	REN JUN ET AL: "Troglitazone attenuates high-glucose-induced abnormalities in relaxation and intracellular calcium in rat ventricular myocytes." DIABETES, vol. 45, no. 12, 1996, pages 1822-1825, XP001028259 ISSN: 0012-1797 abstract page 1825, column 1, paragraph 1	1-5

-/--

INTERNATIONAL SEARCH REPORT

Int ial Application No
PCT/GB 00/02347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOMINGUEZ LIGIA J ET AL: "Troglitazone prevents abnormalities in myocyte *relaxation in an in vitro model of* diabetic cardiomyopathy." HYPERTENSION (DALLAS), vol. 28, no. 3, 1996, page 541 XP001028260 50th Annual Conference and Scientific Sessions of the Council for High Blood Pressure Research;Chicago, Illinois, USA; September 17-20, 1996 ISSN: 0194-911X abstract	1-5
X	GINSBERG H. ET AL: "A review of metabolic and cardiovascular effects of oral *antidiabetic agents: Beyond glucose-level* lowering." JOURNAL OF CARDIOVASCULAR RISK, (1999) 6/5 (337-346). , XP001028568 abstract page 337, column 2, paragraphs 1-3 page 338, column 1, paragraph 5 -page 339, column 2, paragraph 2; table 1 page 340, column 1, paragraph 4 page 344	1-7
X	SUBRAMANIAM S.: "The emerging role of thiazolidinediones in the treatment of diabetes - mellitus and related disorders." CLINICAL AND EXPERIMENTAL HYPERTENSION, (1999) 21/1-2 (121-136). , XP001028567 abstract; figure 1 page 130, paragraph 3 -page 133, paragraph 3	1-7
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1997 GHAZZI MAHMOUD N ET AL: "Cardiac and glycemic benefits of troglitazone treatment in NIDDM." Database accession no. PREV199799461185 XP002178559 abstract & DIABETES, vol. 46, no. 3, 1997, pages 433-439, *ISSN: 0012-1797*	1-5

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-4 relate to a compound/use defined by reference to the following parameter(s):
P1: a PPARgamma agonist.

The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds specifically mentioned in the claims in relation to the claimed disorders.

Remark: The expression "Compound (I)" in claims 1,5,6 should be replaced by the corresponding chemical name.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int nal Application No
PCT/GB 00/02347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9805331 A	12-02-1998	AU 4050797 A	25-02-1998
		EP 0930882 A2	28-07-1999
		WO 9805331 A2	12-02-1998
US 5902726 A	11-05-1999	US 5994554 A	30-11-1999
WO 0004889 A	03-02-2000	AU 5053599 A	14-02-2000
		AU 5053799 A	14-02-2000
		BR 9912117 A	10-04-2001
		BR 9912144 A	03-04-2001
		CN 1310619 T	29-08-2001
		CN 1310620 T	29-08-2001
		EP 1098638 A1	16-05-2001
		EP 1098639 A1	16-05-2001
		WO 0004889 A1	03-02-2000
		WO 0004890 A1	03-02-2000
		NO 20010292 A	08-03-2001
		NO 20010293 A	07-03-2001
WO 9959586 A	25-11-1999	AU 4005299 A	06-12-1999
		WO 9959586 A1	25-11-1999
WO 9405659 A	17-03-1994	AP 513 A	30-07-1996
		AT 182147 T	15-07-1999
		AU 674880 B2	16-01-1997
		AU 4973093 A	29-03-1994
		BR 1100916 A3	04-07-2000
		CA 2143849 A1	17-03-1994
		CN 1101911 A ,B	26-04-1995
		CN 1183275 A ,B	03-06-1998
		CN 1183413 A ,B	03-06-1998
		CN 1183276 A ,B	03-06-1998
		CZ 9500565 A3	15-11-1995
		DE 69325658 D1	19-08-1999
		DE 69325658 T2	30-12-1999
		DK 658161 T3	29-11-1999
		EP 0658161 A1	21-06-1995
		EP 0960883 A1	01-12-1999
		ES 2133410 T3	16-09-1999
		FI 951004 A	03-03-1995
		FI 982413 A	06-11-1998
		WO 9405659 A1	17-03-1994
		GR 3030794 T3	30-11-1999
		HK 1012363 A1	05-05-2000
		HU 72639 A2	28-05-1996
		IL 106904 A	30-09-1997
		JP 11147885 A	02-06-1999
		JP 2828777 B2	25-11-1998
		JP 8501095 T	06-02-1996
		LU 90712 A9	12-03-2001
		MX 9305397 A1	31-01-1995
		NO 950852 A	03-03-1995
		NO 974646 A	03-03-1995
		NZ 255505 A	22-08-1997
		PL 307812 A1	26-06-1995
		RU 2128179 C1	27-03-1999
		SG 48302 A1	17-04-1998
		SI 9300452 A	30-06-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ›nal Application No
PCT/GB 00/02347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405659 A		SK 27795 A3	09-08-1995
		TW 385309 B	21-03-2000
		US 5741803 A	21-04-1998
		US 5910592 A	08-06-1999
		ZA 9306509 A	16-06-1994